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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,289	08/05/2003	Amy Mae Bunker	PC25244A	7984
28880	7590	01/21/2005	EXAMINER	
WARNER-LAMBERT COMPANY			HUANG, EVELYN MEI	
2800 PLYMOUTH RD			ART UNIT	PAPER NUMBER
ANN ARBOR, MI 48105			1625	

DATE MAILED: 01/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/634,289	BUNKER ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Evelyn Huang	1625	

— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 18 October 2004.  
 2a) This action is **FINAL**.                            2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-12 is/are pending in the application.  
 4a) Of the above claim(s) 3 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,2,4-7,9 and 11 is/are rejected.  
 7) Claim(s) 8,10 and 12 is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
     1. Certified copies of the priority documents have been received.  
     2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
     3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)                            4) Interview Summary (PTO-413)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)                            Paper No(s)/Mail Date. \_\_\_\_\_.  
 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
     Paper No(s)/Mail Date \_\_\_\_\_                                    5) Notice of Informal Patent Application (PTO-152)  
     6) Other: \_\_\_\_\_.

**DETAILED ACTION**

1. Claims 1-12 are pending.

***Election/Restrictions***

2. In response to the restriction requirement mailed on 9-14-2004, Applicants have elected without traverse the invention of Group II, claims 1, 2, 4-12 in part, drawn to a naphthyridine compound (i.e. Y=C(O), CH<sub>2</sub> or CHR<sub>7</sub>, W<sub>1</sub> is CHR<sub>5</sub> or CR<sub>5</sub>, one of W<sub>2</sub>-W<sub>4</sub> is N) the composition and method of use thereof. Claims of Groups I, III-X are withdrawn from further consideration as being drawn to the non-elected inventions.

In the previous office action, the recitation that one of W<sub>2</sub>-W<sub>4</sub> can be NR<sub>5</sub> is an error as Applicants point out in the reply. A correction is hereby made. One of W<sub>2</sub>-W<sub>4</sub> can only be N.

Amending the claims to the elected subject matter is recommended.

***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 4, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Hadley et al.(6245778). The species compounds of claim 2 (columns 22-23), and the pharmaceutical composition thereof, are encompassed by the instant wherein Q is NR<sub>6</sub>C(O), R<sub>1</sub> is substituted phenyl, Y is CH<sub>2</sub> and R<sub>2</sub> is alkyl.

5. Claims 1, 2, 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohno et al. (5367078). The example compounds 58-61, 63-78 (columns 33-36, Table 4), and the pharmaceutical composition thereof, are encompassed by the instant wherein R<sub>1</sub> is optionally

substituted phenyl or heteroaryl, R3 is OH (which tautomerize to oxo ), Q is oxadiazolyl, Y is CH<sub>2</sub>, and R2 is phenylalkyl.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-7, 9, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using the compound of claim 8, does not reasonably provide enablement for compounds wherein two adjacent, substantially sp<sup>2</sup> carbon atoms together form a ring. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. \*\*\*.

a. *Nature of the invention*

The instant invention is drawn to a naphthyridine compound as an inhibitor of matrix metalloprotease for treating osteoarthritis or rheumatoid arthritis.

b. *State of the prior art and the level of the skill in the art*

Matrix metalloprotease encompasses collagenases I, II, III (MMP-1, MMP-8, MMP-13) stromelysin 1, 2, 3 (MMP-3, MMP-1, MMP-11), gelatinase A, B (MMP-2, MMP-9) etc. Inhibitors of collagenase, stromelysin and gelatinase, have been described (Morphy et al. Current Medicinal Chemistry, 1995, 2(3): 743-762). Some inhibitors are selective for certain metalloprotease.

The level of the skill in the art in the metalloprotease field is high.

c. *Predictability/unpredictability of the art*

The high degree of unpredictability is well recognized in the enzyme inhibitor art. A slight change in the structure of the compound would drastically alter the biological activity as

evidenced in the very different IC<sub>50</sub> values among the structurally similar inhibitors for collagenase or stromelysin (Morphy, pages 755-766, Tables 8-11).

d. *Amount of guidance/working examples*

The preparation of examples is limited to compounds wherein Q is C=C, R1 is phenylalkyl or imidazoylmethyl, or triazoloyl methyl. The compounds having substituents wherein two adjacent, substantially sp<sub>2</sub> carbon atoms together form a ring have not been described. Starting material and the process of making the instantly claimed compounds other than the example compounds, especially those wherein two adjacent, substantially sp<sub>2</sub> carbon atoms together form a ring are not seen but required. Absent sources, the public is offered mere language, rather than enablement. *Ex parte Moersch* 104 USPQ 122. *In re Howarth* 210 USPQ 689.

The procedures for in vitro inhibition of MMP-13, procedures of monosodium iodoacetate induced-osteoarthritis in rat model, procedures for the induction of experimental osteoarthritis in rabbit have been described.

e. *Breadth of the claims.*

Applicant's assertion that all the structurally diverse compounds in the generic claims (especially those wherein two adjacent, substantially sp<sub>2</sub> carbon atoms together form a ring and those wherein the substituents are further substituted by multiple cyclic substituents) are effective metalloprotease inhibitors for the treatment of osteoarthritis or rheumatoid arthritis by does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability of the art and the limited working examples (paragraphs b to d above).

f. *Quantitation of undue experimentation*

Since insufficient teaching and guidance have been provided in the specification (paragraphs b to e above), one of ordinary skill in the art, even with relatively high level of skill, would not be able to make and use all the compounds as claimed without undue experimentation.

***Allowable Subject Matter***

7. Claims 8, 10, 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

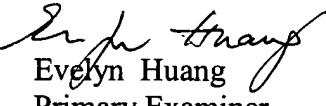
Hadley et al (6245778) or Ohno et al (5367078) fails to teach or suggest the instant alkynyl as Q. Motivation to replace Hadley's amide or Ohno's oxadiazolyl with the instant alkynyl is lacking.

Bunker et al. (US 2004/0038959) has the same priority date as the instant and is therefore not prior art. Bunker's compound has a CH, whereas the instant has a C(O), CH2 or CHR2 as Y. Absent is the motivation to modify Bunker's compound to arrive at the instant invention.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1625